Individual variation in plasma cholesterol response to dietary saturated fat

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See p1251, 1255

Abstract

***Objective*—To determine the extent to which plasma lipid concentrations of individuals are consistently sensitive to changes in saturated fats; to examine whether groups that consistently have large or small responses can be defined; and to identify factors which predict response of lipids to dietary change.**

***Design*—A double crossover design in which two diets (S, providing 21% energy from saturated fat, and P, providing 10%) were followed for periods of six weeks in the sequence SPSP or PSPS.**

***Setting*—67 free living subjects, total cholesterol 5·5-7·9 mmol/l.**

***Main outcome measures*—Relation of cholesterol responses to repeated dietary changes and of potential predictors and cholesterol response.**

***Results*—Similar average changes in cholesterol mask a wide range of individual responses. Response was not related to compliance. In all participants the change in cholesterol observed when the nature of dietary fat was changed on the two crossovers was correlated (r=0·31, P=0·01); the degree of correlation between the two sets of responses was greater in the 46 consistent responders than in the 21 variable responders (r=0·71 *v* r=0·21). Mean differences in cholesterol between diet S and diet P during the two crossovers were 1·16 (SD 0·35) mmol/l and 0·95 (0·26) mmol/l for consistent hyperresponders and 0·18 (0·26) mmol/l and 0·18 (0·25) mmol/l for consistent minimal responders. In consistent responders, changes in total cholesterol in response to increasing saturated fats correlated with baseline cholesteryl ester transfer activity (r=0·32, P=0·03); total cholesterol (r=0·37, P=0·01); triglycerides (r=0·30, P=0·04); and apolipoprotein B (r=0·54, P=0·01).**

***Conclusions*—There is a degree of consistency in cholesterol response to instructions to change dietary fat which is not explained by dietary compliance, and there are groups of consistent hyperresponders and minimal responders within a population of hypercholesterolaemic individuals. Several factors predicting response have been identified. These results have relevance to dietary approaches aimed at reducing the lipoprotein mediated risk of coronary heart disease.**

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BMJ 1995;311:1260-4

Introduction

High concentrations of total cholesterol and low density lipoprotein cholesterol are important determinants of risk of coronary heart disease in populations and individuals.[1-3] Intake of saturated fatty acids is the most important dietary determinant of total cholesterol and low density lipoprotein cholesterol in populations and groups of people.[4-6] There is controversy, however, regarding whether some individuals respond more than others to changes in dietary saturated fatty acids and whether genetic or clinical attributes can distinguish "diet sensitive" from "diet insensitive" individuals.[7-14] Most previous studies to assess response have included small groups of selected subjects; have investigated a single dietary crossover, rather than repeated challenges[8-10]; or have been based on retrospective data.[8 12 14] We challenged a group of 67 volunteers with a change in nature of dietary fat on two occasions to determine whether plasma lipid concentrations are consistently sensitive to changes in saturated fats and to examine whether it is possible to identify a group of people who consistently have a large or small response. We also attempted to identify factors predicting extent of response.

Methods

SUBJECTS, DIETS, AND EXPERIMENTAL DESIGN

The study involved a randomised double crossover trial of two dietary interventions in free living individuals eating usual foods and continuing their usual activities. Ethical approval was obtained from the ethics committee of the Otago Area Health Board and written consent was obtained from each subject. Seventy two people aged 26-64 years with plasma cholesterol concentration 5·5-7·9 mmol/l, triglyceride concentration below 3 mmol/l, and not taking drugs known to influence lipid metabolism were included in the study. Sixty seven participants (28 men, 39 women) completed the study. During a five week run in period the participants consumed their usual diets and completed a five day food diary.

Subjects were randomised to one of two dietary sequences, SPSP or PSPS. Each phase (S or P) of the double crossover was continued for six weeks. Diets were individually constructed. The two intervention diets (S and P) were isoenergetic, with energy content calculated from the baseline diet record. On both diets protein provided about 15% energy, carbohydrate 47%, and fat 38%, but fat composition differed. In diet S, 26% energy came from saturated fatty acids, 10% from monounsaturated fat, and 2% from polyunsaturated fatty acids. In diet P, saturated fatty acids provided 9% energy, polyunsaturated fatty acids 23%, and monounsaturated fat 6%. Foods containing fat provided approximately 20% dietary fat and were similar on the two diets.

Exchange lists were provided to enable participants to select appropriate foods. The test fat (butter and coconut oil in diet S; polyunsaturated margarine and safflower oil in diet P) provided 80% fat energy. Addition of egg yolk to diet P helped to ensure similar cholesterol intakes with both diets. Detailed instructions, menus, and recipes were provided and were reinforced during regular interviews and telephone calls.

Compliance was assessed by five day diet records during each of the four intervention periods (nutrient intake computed using New Zealand Food Composition database [15]) and by measurement of the fatty acid composition of erythrocyte membrane phospholipid and plasma phospholipids and triglycerides at baseline and during one period of diet S and diet P in 36 randomly selected subjects.

Before randomisation (at baseline) and at weeks 4 and 6 of each diet period, weight was recorded and a fasting blood sample taken. Blood specimens were separated by centrifugation at 3000 rpm at 4°C and aliquots of plasma stored at −20°C for lipid and lipoprotein analysis. Aliquots of plasma from the

baseline visit were stored at −80°C for determinations of cholesteryl ester transfer activity.

LABORATORY METHODS

Cholesterol concentration in plasma and lipoprotein fractions was measured enzymatically using Boehringer kits and calibrators, and triglyceride concentration was measured enzymatically using Roche Diagnostics kits on a Cobas Fara analyser. Coefficient of variation was 1·6% for cholesterol and 3·4% for triglycerides in the Royal Australasian College of Pathologists' quality assurance programme. High density lipoprotein cholesterol was measured in the supernatant after lipoproteins containing apolipoprotein B were precipitated with phosphotungstate and magnesium chloride solution.[16] Low density lipoprotein cholesterol concentration was calculated with the Friedewald formula.[17] Transfer of newly synthesised cholesteryl esters was measured in plasma with an isotopic assay, coefficient of variation 10%.[18] Plasma cholesteryl ester transfer activity is closely related to cholesteryl ester mass transfer measured by chemical methods[19]; it was not significantly altered by storage of plasma at −80°C for one month. The apoE phenotype was determined by isoelectric focusing of very low density lipoprotein apoproteins by modification of a published method.[20] Phospholipid fatty acids were extracted from erythrocytes of stored blood treated with EDTA[21] and phospholipid and triglyceride fatty acids were extracted by the Folch method.[22] Methyl esters of fatty acids were separated on a Hewlett Packard gas chromatograph by using an Alltech FFAP Econo-cap capillary column and fatty acid peaks were identified by using Nu Check standards. Apolipoprotein A_1 and apolipoprotein B were measured by immunoturbimetry by using Boehringer kits (coefficient of variation 2·6% and 6%).

STATISTICAL ANALYSIS

Lipoprotein measurements made at week 4 and week 6 were not significantly different so the mean of the two values was used in most subsequent calculations. Analysis of variance (ANOVA) with repeated measures was used to analyse dietary and lipid data. The analysis compared two factors: the high and low saturated fat diets (P1, P2 *v* S1, S2) and the two crossovers (P1, S1 *v* P2, S2) and the interaction between these two factors. Individual diet phases (for example, P1 *v* S1) were compared with paired *t* tests, and subgroups (for example, men *v* women) were compared with independent *t* tests or with ANOVA (for example, for comparing the groups defined according to degree of response). Three of the measured variables (P:S ratio, triglycerides, very low density lipoprotein cholesterol) did not follow a normal distribution and were log transformed before analysis. Responsiveness to diet was calculated for each subject as the difference between total cholesterol concentration on the diet high in saturated fat (diet S) and the diet low in saturated fat (diet P)—that is, for the first crossover ΔTC1 (in mmol/l)=TC(S1)−TC(P1) and for the second crossover ΔTC2=TC(S2)−TC(P2). Means (SD) were calculated for these differences. Coefficient of variation (CV−(SD+mean)×100%) was used to describe degree of variability of individual changes in cholesterol.

"Consistent" responders were defined as those whose difference in total cholesterol (ΔTC1− ΔTC2) was within one standard deviation of the mean for all participants, the remainder were "variable" responders. Mean difference was calculated ((ΔTC1+ ΔTC2)/2) for consistent responders, and this statistic was used (by using Pearson's correlation coefficient) to identify potential predictors of cholesterol response. Subjects were defined as consistent hyperresponders if change in cholesterol during both crossovers was greater than 10% and as minimal responders if change was less than 10%. The differences between weeks 4 and 6 for subjects on the same diets provided an estimate of biological plus analytical error; these are presented alongside differences in cholesterol response to the diets for comparison.

TABLE I—*Mean (SD) nutrient intake at baseline and during diets low (P1, P2) and high (S1, S2) in saturated fat*

	Baseline	First crossover		Second crossover	
		P1	S1	P2	S2
Energy (kJ/day)	8866 (2449)	8383 (1814)	8845 (1840)	9076 (2415)	9076 (2092)
Protein (% energy)	15 (2)	15 (3)	14 (2)	14 (2)	15 (3)
Carbohydrate (% energy)	50 (6)	48 (7)	46 (6)	48 (6)	46 (7)
Dietary fibre (g/day)	29 (18)	26 (8)	28 (9)	27 (8)	29 (13)
Total fat (% energy)	34 (7)	36 (6)	38 (7)	37 (4)	39 (7)
Saturated (% energy)	14 (4)	10 (2)	21 (5)	10 (2)	21 (6)*
Polyunsaturated (% energy)	5 (2)	13 (4)	4 (1)	12 (4)	4 (1)†
Monounsaturated (% energy)	11 (2)	11 (2)	10 (2)	11 (2)	10 (2)
P:S ratio†	0·4 (0·2)	1·4 (0·6)	0·2 (0·1)	1·2 (0·5)	0·2 (0·1)†
Cholesterol (mg/day)	280 (112)	192 (72)	282 (94)	230 (106)	279 (88)‡

*Values significantly greater on S1 and S2 than P1 and P2, P<0·001.
†Values significantly greater on P1 and P2 than S1 and S2, P<0·001.
‡Values significantly lower on P1 than S1, P<0·01; values significantly lower on P2 than S2, P<0·05.

TABLE II—*Mean (SD) concentrations of total, low density lipoprotein and high density lipoprotein cholesterol and plasma triglycerides during diets high (S1, S2) and low (P1, P2) in saturated fat*

	Baseline	First crossover		Second crossover	
		P1	S1	P2	S2
Cholesterol (mmol/l):					
Total cholesterol*	6·29 (0·78)	5·78 (0·66)	6·41 (0·82)	6·04 (0·73)	6·64 (0·80)
High density lipoprotein cholesterol*†	1·43 (0·31)	1·41 (0·34)	1·50 (0·36)	1·45 (0·33)	1·48 (0·34)
Low density lipoprotein cholesterol*	4·12 (0·78)	3·76 (0·71)	4·27 (0·77)	3·94 (0·75)	4·42 (0·76)
Triglycerides (mmol/l)*‡	1·63 (1·09)	1·51 (0·64)	1·53 (0·67)	1·51 (0·81)	1·75 (0·90)

*Values higher on S1 and S2 than P1 and P2, P<0·001.
†Change in high density lipoprotein cholesterol greater during first crossover than during second crossover, P<0·05.
‡Change in total cholesterol greater during second crossover than during first crossover, P<0·01.

Results

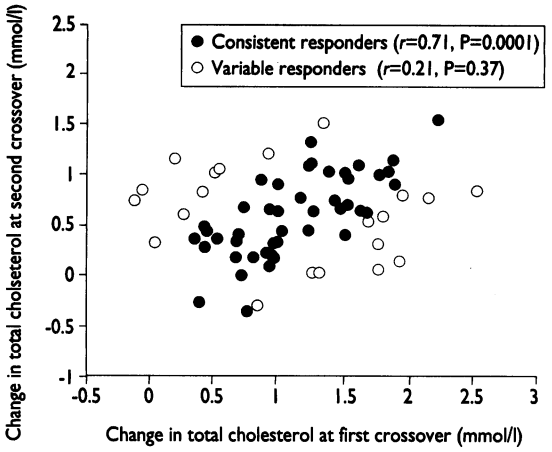
Body weight (mean 73 (SD 14·2) kg) remained constant. Table I shows energy and nutrient intakes calculated from diet records. There seemed to be a high level of compliance with dietary advice. Intakes of saturated fatty acids were approximately halved in the two periods of diet P compared with the two periods of diet S, and P:S increased from 0·2 to >1. Reported intakes of saturated fatty acids were comparable in the two P and the two S periods. Fatty acid composition of erythrocyte membrane phospholipids and of plasma triglyceride and phospholipid mirrored the reported dietary changes. For example, in erythrocyte membrane phospholipid, the proportion of myristic acid was significantly lower during P than S (mean 0·4% (SD 0·1%) *v* 0·8% (0·2%), P<0·001) and linoleate was significantly higher (8·7% (1·2%) *v* 7·2% (0·9%), P<0·001). Triglyceride linoleate comprised 18·5% (6·6%) of total fatty acids in diet P compared with 8·4% (3·2%) in diet S (P<0·001). There were no differences in reported dietary intake, fatty acid composition of red cell membrane, or plasma lipids in the consistent and variable response groups or between consistent hyperresponders and minimal responders.

Total cholesterol and low density lipoprotein cholesterol concentrations were significantly higher (P<0·001) on the diets high in saturated fatty acids (S1 and S2) than on the diets low in saturated fatty acids (P1 and P2). Concentrations in diets S1 and S2 were similar to those observed with the baseline diet (table II). The between person coefficient of variation for change in total cholesterol was 94·4% (−0·63 to 2·03 mmol/l) for the first crossover and 70·2% (−0·38 to 1·91 mmol/l) for the second crossover.

In the group as a whole the correlation between these changes was 0·31 (P=0·01) (figure). In the 46 consistent responders the correlation between the changes was striking (r=0·71, P=0·0001); the correlation in the 21 variable responders was not significant (r=0·21, P=0·37).

Table III shows cholesterol changes in consistent hyperresponders and consistent minimal responders contrasted with differences between values at week 4 and week 6 on each diet; this analysis provides an indication of biological and analytical error. Consistent hyperresponders differed appreciably from minimal responders with respect to baseline cholesteryl ester transfer activity, total cholesterol concentration, and lipoproteins containing apolipoprotein B (that is, low density lipoprotein cholesterol and very low density lipoprotein cholesterol) (table IV).

The mean change in total cholesterol concentration was significantly correlated with baseline plasma cholesteryl ester transfer activity and concentrations of triglycerides, total cholesterol, and apolipoprotein B (table V). Mean change in total cholesterol was not significantly associated with age, initial body mass index, and reported increase in dietary saturated fatty acids; on the two crossovers it did not differ significantly in men and women (0·59 (0·46) *v* 0·63 (0·38) mmol/l, P=0·74). Plasma cholesteryl ester transfer activity was significantly correlated with baseline concentrations of plasma triglyceride (r=0·64), very low density lipoprotein cholesterol (r=0·50), and high density lipoprotein cholesterol (r=−0·59) (all P<0·001) and apolipoprotein B and total cholesterol (r=0·63 and r=0·60 respectively, P<0·01).



Scattergram for individual change in total cholesterol between first and second crossover

The small number of participants with the apoE4 allele (nine had the 4/4, 4/3, or 4/2 phenotype; whereas 31 had the 3/3 or 3/2 phenotype) precluded detailed consideration of the extent to which apoE phenotype influenced response. Nevertheless it is of interest to note that mean change in total cholesterol for those with the apoE4 allele was 0·85 (0·45) mmol/l, whereas in those with the apoE3/3 or 3/2 phenotype it was 0·59 (0·38) mmol/l (P=0·09).

TABLE III—*Mean (SD) differences in cholesterol during the two crossover periods, contrasted with the differences in cholesterol between weeks 4 and 6 as an indicator of biological and analytic "error"*

	Consistent hyperresponders (n=25)	Consistent minimal responders (n=21)	Variable responders (n=21)	P value (ANOVA)
Change in total cholesterol:				
First crossover*	1·16 (0·35)	0·18 (0·26)	0·49 (0·59)	0·0001
Second crossover*	0·95 (0·26)	0·18 (0·25)	0·61 (0·35)	0·0001
Mean difference in cholesterol between weeks 4 and 6:				
Diet S	0·11 (0·31)	0·14 (0·38)	0·19 (0·44)	0·7843
Diet P	0·09 (0·34)	0·08 (0·42)	0·01 (0·53)	0·4755

*All differences between groups significant at 0·1% level (Student's *t* test).

TABLE IV—*Mean (SD) baseline characteristics in consistent and variable responders*

	Consistent responders			
	Hyperresponders (n=25)	Minimal responders (n=21)	Variable responders (n=21)	P value (ANOVA)
Age (years)	51 (8)	52 (8)	51 (10)	0·90
Body mass index (kg/m²)	25 (3)	26 (4)	25 (3)	0·82
Cholesterol ester transfer activity (nmol/ml/hr)	29·0 (10·3)	22·0 (5·5)	24·8 (10·2)	0·04*†
Cholesterol (mmol/l):				
Total	6·5 (0·73)	5·8 (0·64)	6·4 (0·62)	0·04*†
High density lipoprotein	1·36 (0·29)	1·51 (0·26)	1·39 (0·33)	0·20
Low density lipoprotein	4·28 (0·91)	3·72 (0·57)	4·23 (0·73)	0·48
Very low density lipoprotein	0·75 (0·63)	0·51 (0·46)	0·72 (0·21)	0·25
Low and very low density lipoprotein	5·03 (0·73)	4·23 (0·71)	4·96 (0·82)	0·01*†
Triglyceride (mmol/l)	1·8 (1·26)	1·2 (0·91)	1·7 (1·10)	0·13
Apolipoprotein B (mg/dl)	144·5 (35)	99·5 (24·7)	135·5 (47)	0·01*†

*Consistent hyperresponders *v* consistent minimal responders, P<0·01.
†Variable responders *v* minimal responders, P<0·05.

TABLE V—*Relation of baseline variables and mean change in total cholesterol for consistent responders (n=46)*

Baseline variable	Pearson's correlation coefficient	Probability
Age (years)	−0·01	0·93
Body mass index (kg/m²)	0·02	0·90
Height (m)	0·02	0·89
Weight (kg)	0·03	0·86
Cholesteryl ester transfer activity (nmol/ml/hr)	0·32	0·03
Cholesterol (mmol/l):		
Total	0·37	0·01
High density lipoprotein	−0·27	0·08
Low density lipoprotein	0·24	0·11
Very low density lipoprotein	0·26	0·08
Triglyceride (mmol/l)	0·30	0·04
Apolipoprotein A_1 (mg/dl)	−0·14	0·34
Apolipoprotein B (mg/dl)	0·54	0·01

Discussion

Several studies have examined the extent to which lipids and lipoproteins consistently respond to changes in dietary cholesterol,[23 24] but few[7–14] have examined response to dietary saturated fatty acids, which have more powerful effects than intake of cholesterol on total cholesterol and low density lipoprotein cholesterol concentration. We have shown that there is appreciable individual variation in response of total cholesterol and low density lipoprotein cholesterol to changes in dietary saturated fatty acids which is not explained by variation in compliance, as assessed by diet record and plasma lipid fatty acid composition. This response tends to be consistent, and groups who consistently show a large or small response can be defined. Some predictors of response have been identified.

This study included a large number of individuals at relatively high lipoprotein mediated risk of coronary heart disease because of moderately raised concentrations of total cholesterol and low density lipoprotein cholesterol, whereas most earlier investigations included smaller numbers of normolipidaemic subjects.[10 13 14] Rather than a single challenge, we used two periods in which high and low saturated fatty acid diets were contrasted. Both our methods for assessing changes in nature of dietary fat showed that as a group there was a high degree of dietary compliance in these motivated volunteers. These features of this study have enabled us to draw firm conclusions.

In regard to average response to changes in the nature of fat, total cholesterol responses were consistent between first and second crossovers and within the range predicted.[14] Though individual responses varied widely (a finding earlier reported by Grundy and colleagues[8]), we found a convincing relation between response of cholesterol to dietary changes on two separate occasions. Although dietary cholesterol intake was lower when intake of saturated fat was low (P1, P2)

than when it was high (S1, S2), two observations suggest that the differences in total cholesterol and low density lipoprotein cholesterol were principally due to changes in type of dietary fat. Firstly, differences in dietary cholesterol were greater during the first crossover than the second, yet differences in total cholesterol and low density lipoprotein cholesterol were similar during the two crossovers. Secondly, cholesterol intake was relatively low and in the range where changes in intake would not be expected to have a major effect on plasma cholesterol concentrations.[25]

RESPONSE TO CHANGES IN DIET

Previous studies have used arbitrary criteria to classify response to changes in dietary fat and cholesterol intake.[9 13] Having carried out a double crossover study we were able to classify individual response as "consistent" or "variable" to the two diet crossovers, depending on whether or not difference in total cholesterol response (ΔTC1 – ΔTC2) was within one standard deviation of the mean for all participants. We then adopted the widely used 10% cut point to identify consistent minimal responders and hyperresponders. The appreciable and similar magnitudes of cholesterol responses to diet on both crossovers among the consistent hyperresponders provides evidence for the existence of a group of people who show a consistently large response to change in dietary fat. The consistent minimal responders, on the other hand, showed a difference in response that did not differ from that expected from biological and analytical variation (table III). Variable responders might have had a degree of compliance less than did the consistent responders, although not measurably so, as suggested by the data in table IV, which show that characteristics of variable responders are closer to those of hyperresponders than minimal responders.

The variation in response presumably reflects an interaction between polygenic and other factors. Certain apolipoprotein B and E genotypes have been identified as conferring the characteristic of hyperresponse of blood cholesterol to dietary cholesterol[26–29] and saturated fatty acids. The suggestion in our data that the apoE4 allele may be associated with hyperresponse is compatible with previous findings,[27] though the small number of subjects with apoE4 and E2 alleles preclude definitive conclusions. Genetic variations in the apolipoprotein B gene,[26 30 31] initial total cholesterol and triglyceride concentrations, body mass index, age, and sex have previously been suggested as predictors of cholesterol response to dietary change.[8 9 12 13] Our study, which was larger than most previous ones and the first to include a double crossover design, has confirmed that initial cholesterol, apolipoprotein B, and triglyceride concentrations are predictors (tables IV and V).

EFFECT OF CHOLESTERYL ESTER TRANSFER ACTIVITY

A new observation in this study is the association between plasma cholesteryl ester transfer activity at baseline and cholesterol response to change in dietary fat. There are several possible explanations for an effect of cholesteryl ester transfer activity on total cholesterol and low density lipoprotein cholesterol. Low cholesteryl ester transfer activity could enrich low density lipoprotein cholesterol precursor particles with apolipoprotein E,[32] which may increase their clearance by hepatic receptors, thereby reducing formation of low density lipoprotein cholesterol. Reduced transfer of cholesteryl esters to chylomicrons and very low density lipoprotein cholesterol remnants, which are cleared by the liver, may reduce hepatic cholesterol content and subsequently increase activity of low density lipoprotein cholesterol receptors and uptake of circulating low density lipoprotein cholesterol. Raised plasma cholesteryl ester transfer activity will presumably have the opposite effect. On the other hand, the association between baseline cholesteryl ester transfer activity and the response of plasma cholesterol to change in dietary fat may be mediated by baseline concentrations of lipoproteins containing apolipoprotein B, which were correlated with both variables. These lipoproteins are acceptors of cholesteryl esters transferred from high density lipoprotein cholesterol, and variation in their concentration may therefore modulate cholesteryl ester transfer activity.

CONCLUSION

These findings provide evidence of a reproducible individual variation in cholesterol response to changes in dietary fat and for the existence of groups that consistently show large and small responses to dietary change. The results are not explained by variable dietary compliance and may be determined by cholesteryl ester transfer activity, apolipoprotein B concentrations, and other polygenic factors. Although the arguments in favour of the population approach to dietary change remain strong,[33] these data provide evidence for concurrent emphasis on the individual approach, which attempts to identify individuals at risk who are likely to benefit greatly from targeted dietary advice.

Key messages

- Dietary saturated fatty acids have more powerful effects than intake of cholesterol on plasma cholesterol concentrations
- Individual variation in response of lipid concentrations to changes in dietary saturated fatty acids tends to be consistent
- The apoE4 allele may be associated with consistent hyperresponse
- Initial cholesterol concentration and concentrations of apolipoprotein B and triglycerides are predictors of cholesterol response to dietary change in saturated fatty acids
- Plasma cholesteryl transferase activity at baseline is associated with response to change in dietary fat

We gratefully acknowledge the cooperation of participants in the study and the excellent technical and research assistance of members of the lipid research team, including Alex Chisholm, Ashley Duncan, Dean Hackett, Barbara McSkimming, Ross Marshall, Sylvia Stapley, and Margaret Waldron. We are also indebted to Dr Chris Frampton for his expert statistical assistance.

Funding: National Heart Foundation of New Zealand and the Anderson and Telford Charitable Trust.

Conflict of interest: None.

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(Accepted 8 September 1995)

Health effects of anticipation of job change and non-employment: longitudinal data from the Whitehall II study

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See p 1282, 1285

Abstract

***Objective*—To assess the effect of anticipating job change or non-employment on self reported health status in a group of middle aged male and female white collar civil servants.**

***Design*—Longitudinal cohort study (Whitehall II study). Questionnaire data on self reported health status and health behaviour were obtained at initial screening and four years later, during the period when employees of the department facing privatisation were anticipating job change or job loss.**

***Setting*—London based office staff in 20 civil service departments.**

***Subjects*—666 members of one department threatened with early privatisation were compared with members of the 19 other departments.**

***Main outcome measures*—Self reported health status measures and health related behaviours, before and during anticipation of privatisation.**

***Results*—In comparison to the remainder of the cohort, the profile of health related behaviours of cohort members who faced privatisation was more favourable, both before and during anticipation of privatisation. There were no significant differences in the changes in health behaviours between cohort members moving into a period of job insecurity and the remainder of the cohort. Self reported health status, however, tended to deteriorate among employees anticipating privatisation when compared with that of the rest of the cohort.**

***Conclusions*—The application of a longitudinal design, allowing the same individuals to be followed from job security into anticipation, provides more robust evidence than has previously been available that anticipation of job loss affects health even before employment status has changed.**

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BMJ 1995;311:1264-9

Introduction

The health consequences of redundancy and unemployment have been investigated since the period of high unemployment in the 1930s.[1] These studies have, in general, shown that unemployment is associated with an increased risk of mortality,[2-4] morbidity,[5-7] and psychological ill health.[8-10] Current unemployment in countries of the Organisation for Economic Co-operation and Development (OECD) is at a postwar high of 35 million, and an estimated further 15 million people have either given up looking for work or unwillingly accepted a part time job.[11] Therefore the potential of unemployment to damage health constitutes an important, and growing, problem.

Anticipation of redundancy or rationalisation is generally referred to as "the anticipation phase" in studies of the effects of job insecurity on health. It is often cited as being similar in effect on health to unemployment, but few studies have followed their subjects longitudinally from secure employment and into the phase of anticipation of job change or job loss. Furthermore, many previous studies of redundancy have lacked a control group of any kind, and even in the few studies where a control group has been included[5,12,13] this has seldom been adequately matched to the group experiencing increasing job insecurity or unemployment.[14]

A major consideration when examining the relation between health and labour market experience is the extent to which the experience of job insecurity and subsequent events is a consequence, rather than a cause, of ill health. During times of economic contraction the least productive members of any workforce are the most likely to be shed. Therefore ill health may itself lead to a greater risk of unemployment. Similarly, for people in poor health, who recognise that their chances of re-employment are reduced, job insecurity may be a more salient and stressful life event. If this is the case, cross sectional studies of self reported levels of job insecurity and health could reveal associations that are of no causal significance. These issues can be resolved only if baseline data are collected before job loss and study participants are followed up through the entire period of change in employment. The ability to perform such